Statistical modelling of time-varying covariates for survival data

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Part I

Pharmacoepidemiology in Heart Failure

Chapter 1

A new method for measuring adherence to polypharmacy

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Heart failure (HF) is a major and growing public health issue, characterized by high costs, steep morbidity and mortality [129]. Despite the advances in the understanding the pathophysiology of chronic HF and the improvement of therapy, HF mortality and morbidity rates remain high [141, 98]. HF guidelines [139, 221, 50] have consistently focused on the benefits of neurohormonal therapy in HF patients with reduced ejection fraction to delay progression and improve survival. These recommendations also underlined up-titration of neurohormonal doses toward target, when possible, by the time of hospitalization discharge. However, medication non-adherence is a common issue, and it is associated with adverse health conditions and increased economic burden to the healthcare system especially in case of chronic diseases such as HF [158].

Recent observations suggest that up to 50% of early post discharge mortality may be associated with guidelines non-adherence [61]. However, previous epidemiological studies of adherence to polypharmacy have analyzed HF patients from surveys of highly selected populations [225]. Further, these studies were based on physician's prescriptions [108, 107] regardless of patients' adherence in the follow up [107]. Several concerns remain on adherence of unselected patients of real world setting to evidence-based HF treatment. To overcome the aforementioned gaps, it is possible to estimate patients' adherence from drugs purchases, and this is particularly feasible in a public health system using healthcare administrative archives. Worth of note, methods for estimating adherence to single drug classes from drugs purchases are well established [102, 14], whereas there are few studies on patient's adherence, especially in the setting of polypharmacy [17]. Specifically, in cardiological literature, focusing both on polypharmacy and on adherence is still an open research field [58, 63].

The present chapter aim is to investigate HF patients' adherence to disease-modifying therapies during the first year after HF hospitalization and to estimate its prognostic impact on survival. First, we describe how evidence-based therapies are applied in a

real world setting, including the evaluation of target dosages based on drugs purchases. Secondly, we represent polypharmacy adherence during the first year as combinations of prescriptions and adherence to the pharmacological classes of interest. In particular, we introduce a novel method for measuring adherence to polypharmacy by computing the ratio between two quantities: the *"Polypharmacy Adherence"* (PA) and the *"Purchase Indicator"* (PI), so producing the *Patient Adherence Indicator* (PAI). Finally, we evaluate the effect of PAI on survival using different Cox models [46], adjusting for demographic characteristics, comorbidities, re-hospitalisations events and patterns of care in the year following the index HF hospitalization.

1.1. Materials and Administrative data

1.1.1. Study setting

Between January 2009 and December 2015, patients hospitalized in the *Friuli Venezia Giulia* Italian Region (FVG, a north-eastern region of Italy, with a population of about 1.2 million inhabitants) with a principal diagnostic code of HF and at least one pharmacological purchase of disease-modifying drugs for HF were recruited. Patients who were not inhabitants of the FVG region or were younger than 18 years at the time of hospitalization were excluded. Enrolment occurred from the data of discharge of HF hospitalization.

1.1.2. Data sources

The data of healthcare administrative archives were used for identification of HF patients. The FVG regional Data Warehouse includes various sources of data, such as the Registry of Births and Deaths, Hospital Discharge, the District Healthcare Services (intermediate and home care), Public Laboratories and Public Drug Distribution System, that are object of internal routinely quality checks. Of note, the availability of laboratory analyses performed in public hospitals is a peculiar characteristic of this Region. Each record in the dataset was related to an event, which could be a HF hospitalization or hospitalization for other causes, an activation of Intermediate Care Unit (ICU) service or an Integrated Home Care (IHC). For all these events (admission to hospital or ICU/IHC), we collected dates of admission and discharge. Moreover, for each HF hospitalization, we identified with a binary flag if the patient was discharged from a Cardiological Ward (CW), if a cardiological visit and an echocardiogram were performed. In the Public Drug Distribution System, each record represented a pharmacological purchase characterized by the date of acquisition, ATC (Anatomical Therapeutic Chemical classification system) [220, 214] and AIC codes (authorization code related to Italian market) [3] and the total number of purchased boxes.

1.1.3. Study population

HF primary diagnosis included ICD-9CM codes for HF (428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91 and 404.93) selected according to the National Outcome Evaluation Program. We focused on those patients with a first discharge (associated with a principal diagnostic code of HF) between January 2009 to December 2015 and we excluded those patients who died during the first HF hospitalization. We defined a 5 *years pre-study period* from 2004 to 2008 (Figure 1.1), in order to observe chronic comorbidities and hospitalizations for HF. This allowed us to limit underestimation of chronic comorbidities and to identify new incident HF patients (those with no hospitalizations for HF during the pre-study time-window). The *study-period* was divided into the *observation period* (365 days from the index discharge date) and the *follow-up period*: only patients alive at the end of the observation period were followed up to observe survival outcomes (Figure 1.1). Finally, only patients with at least one pharmacological purchase related to the disease-modifying drugs were included [139, 50]. Specifically, we considered the following drugs: Angiotensin-Converting Enzyme inhibitors (ACE), Angiotensin Receptor Blockers (ARB) – these two considered as a unique class (ACE/ARB), Beta-Blocking (BB) and Anti-Aldosterone agents (AA).

Patients were classified as *Worsening Heart Failure* (WHF) or *De Novo* on the basis of the presence of at least one HF hospitalization in the 5 years preceding the index HF hospitalization (Figure 1.1). Demographic, comorbidities, procedures and laboratory tests performed during hospitalization were considered. Among procedures, we considered only the major ones as Coronary Angiography, Percutaneous Transluminal Coronary Angioplasty (PTCA) (w/out implantation of stent in coronary artery), Coronary Artery Bypass Graft surgery (CABG), implantation of pacemaker, Cardioverter defibrillator or Cardiac Resynchronization Therapy (CRT), Transcatheter Aortic Valve Implantation (TAVI) or percutaneous mitral valve repair with MitraClip device. Finally, the Charlson Comorbidity Index [160] was computed using hospital diagnoses based on ICD-9CM that occurred within 5 years before the hospitalization and integrated with laboratory data and diagnosis recorded at the hospitalization, as previously reported [59].

In order to protect privacy, information retrieved from the different databases were linked

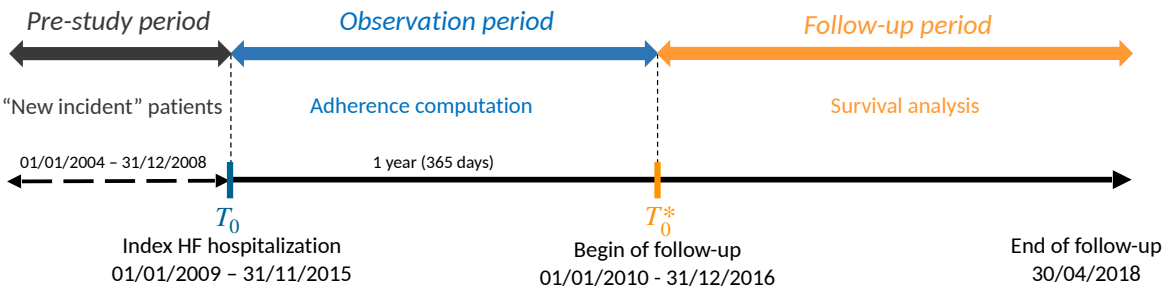

Figure 1.1. Study design for a HF patient of the study cohort. The *pre-study period* is used to define "new incident" HF patients. The *observation period* is used for adherence computation. The *follow-up period* is used for survival analysis. The administrative censoring date is April 30^{th}, 2018.

via a single anonymous identification code by institutional technical staff. The reverse process is not possible since the generation code table is not available to the authors. Data analyses were performed by authorized staff only on remotely controlled computer. Any possibility to copy or export datasets was disabled. According to the rules from the Italian Medicines Agency [5], retrospective studies using administrative databases do not require Ethics Committee protocol approval.

1.2. Methodologies

1.2.1. Target dosages according to guidelines

In order to evaluate if the purchased drug quantity was in line with the expected target dosage, we considered an *observation period* of 365 days starting from the index date and we computed the total purchased milligrams of the main active principles for each pharmacological class of interest. Dividing these quantities by 365, we obtained the mean purchased daily doses (DD) of each active principle. Then, we divided them by the respective target dosages (see Table 1.1) as recommended in the ESC (*European Society of Cardiology*) Guidelines [139, 50] or, for those drugs not included in the guidelines, as prescribed routinely in clinical practice and verified in the Italian Drug Agency's (in Italian: AIFA – *Agenzia Italiana del Farmaco*) website [4]. Thus, we obtained the *standardized Daily Doses* (sDD) that patients assumed during the observation period:

$$\text{sDD} = \frac{\text{mean purchased daily dose (DD) during observation period}}{\text{target dose recommended in ESC or AIFA guidelines}}. \tag{1.1}$$

If the sDD was 100% (i.e., sDD = 1) the mean purchased DD was equal to the perfect target, whereas if it was $<$ or $>$ 100%, it was less or higher than the perfect target, respectively.

1.2.2. Adherence measures

Medication adherence is generally defined as the process by which patients take their medications as prescribed and three different constructs could be analyzed, i.e., *initiation* of therapy, *implementation* of the dosing regimen and *persistence* with treatment [212]. In the present chapter, we focused on *implementation*, according with the review paper [212], basing our analysis on purchased drugs instead of prescribed drugs. According to [102, 14] we calculated two measure of adherence, i.e., the Proportion of Days Covered (PDC), defined as:

$$\text{PDC} = \frac{\text{number of distinct coverage days}}{\text{number of days in the observation period}} \tag{1.2}$$

and the Medical Possession Ratio (MPR):

$$\text{MPR} = \frac{\text{number of days supply during observation period}}{\text{number of days in the observation period}}. \tag{1.3}$$

Table 1.1. Target dosages of each active principle recommended in the ESC (*European Society of Cardiology*) [139, 50] or AIFA (*Agenzia Italiana del Farmaco*) guidelines [4].

Pharmacological class	Active principle	Daily target dose [mg]	Guideline
Anti-Aldosterone agents	Canrenone	50	AIFA
	Potassium Canrenoate	50	AIFA
	Spironolactone	25	ESC
Angiotensin-Converting Enzyme inhibitors	Enalapril	20	ESC
	Lisinopril	20	ESC
	Ramipril	10	ESC
Angiotensin Receptor Blockers	Candesartan	32	ESC
	Losartan	150	ESC
	Olmesartan	40	AIFA
	Telmisartan	80	AIFA
	Valsartan	320	ESC
Beta-Blocking agents	Bisoprolol	10	ESC
	Carvedilol	50	ESC
	Metoprolol	200	ESC
	Nebivolol	10	ESC

The distinction between PDC and MPR consists in the numerator that is different in case of overlapping of two subsequent purchases. In particular, through PDC we considered the period covered by the first purchase entirely and the second purchase only in those days that were not covered by the first one. Conversely, through MPR we shifted the second purchase at the day after the end of the first one, preserving the duration of all purchases.

These measures were dichotomized to identify as adherent those patients with a PDC (or MPR) at least 80% [14]. For adherence computation of each of the disease-modifying pharmacological class (ACE/ARB, BB, AA) an observation period of 365 days from the index date was considered [102]. If during the observation period a patient was re-hospitalized or spent some time in ICU, we assumed that he/she was under treatment, i.e., he/she was taking all the purchased types of drug during those periods.

1.2.3. Adherence to polypharmacy

In order to evaluate polypharmacy, we introduced a new index, the *Patient Adherence Indicator* (PAI), based on the ratio between the *Polypharmacy Adherence* (PA) and the *Purchase Indicator* (PI). These measures are computed using observed combinations of the three pharmacological classes of interest: BB, AA and ACE or ARB. PI is defined as the number of purchased types of drug at least once and it could be 1, 2 or 3 based on patient's different purchases:

$$\text{PI} = \text{number of purchased types of drug at least once.} \tag{1.4}$$

PA is the number of pharmacological classes to which the patient is adherent at the defined threshold of 80% (0, 1, 2 or 3):

$$\text{PA} = (\text{adherent to ACE or to ARB}) + \text{adherent to BB} + \text{adherent to AA}. \tag{1.5}$$

Finally, PAI is the number of pharmacological classes to which the patient is adherent divided by the number of purchased types of drug:

$$\text{PAI} = \frac{\text{PA}}{\text{PI}}. \tag{1.6}$$

PAI considers adherence to polypharmacy and it could be 0, 1/3, 1/2, 2/3 or 1 (3/3). Based on the overall PAI percentage, patients were divided into two groups: those with *poor* adherence percentage to polypharmacy (PAI $< 50\%$, i.e., $< 1/2$) and *good* adherence percentage (PAI $\geq 50\%$, i.e., $\geq 1/2$).

1.2.4. Outcome measure

Study outcome of interest was patient's death for any cause. Deaths were collected from the Registry of Birth and Deaths included in the regional Data Warehouse. For the survival analysis, each patient was followed from one year after the index date (i.e., one year after the discharge from the index HF hospitalization – T_0^* in Figure 1.1) until the end of the study or the date of death (see *follow-up period* in Figure 1.1). The administrative censoring date was April 30$^{\text{th}}$, 2018.

1.2.5. Survival Analysis: multivariable Cox regression models

In order to assess the role of polypharmacy adherence with respect to the overall survival time of a patient, we estimated four different Cox regression models [46], one for each of the following polypharmacy indices: PAI and PAI group, computed with both PDC and MPR adherence measures. Each model was adjusted for nine covariates: WHF condition (`WHF`) and discharge from CW at the index hospitalization (`CW`), cardiological visit in 24 months before the last hospitalization of the observation period (`cardio`), number of re-hospitalizations (`rehosp`), number of ICU services (`ICU`) and IHC activation during the observation period (`IHC`), Charlson index at the last hospitalization of the observation period (`charlson`), age (`age`) and gender (`gender`) at the beginning of the follow-up. The choice of these covariates was driven by clinical relevance and availability from administrative data. The hazard functions for each patient i were hence given by:

$$h_i\left(t|\boldsymbol{\omega}_i\right) = h_0(t)\exp\left\{\boldsymbol{\theta}^T\boldsymbol{\omega}_i\right\} \tag{1.7}$$

where the covariate vector for each patien was

$$\boldsymbol{\omega}_i = (\texttt{WHF}_i, \texttt{age}_i, \texttt{gender}_i, \texttt{charlson}_i, \texttt{CW}_i, \texttt{cardio}_i, \texttt{rehosp}_i, \texttt{ICU}_i, \texttt{IHC}_i, \omega_{10,i})$$

with polypharmacy index $\omega_{10,i}$ equal to

$$\texttt{PAI\_PDC}_i \quad \text{or} \quad \texttt{PAI\_MPR}_i \quad \text{or} \quad \texttt{PAIgroup\_PDC}_i \quad \text{or} \quad \texttt{PAIgroup\_MPR}_i.$$

All the analyses were carried out using the free software R [161], in particular survival package [201, 202]. Covariates with p-values < 0.05 were considered statistically significant.

1.3. Results

Patient characteristics are presented as numbers and percentages for categorical variables. For continuous variables we reported means with standard deviations or medians with interquartile ranges (IQRs), as appropriate depending on the distribution shape.

1.3.1. Cohort selection

A total cohort of 20,622 patients were identified with principal diagnostic code of HF. Of these, we excluded 13 paediatric patients. A substantial portion of patients (6,505, 32%) was not considered because they died during the first year after the index hospitalization. Moreover, 1,020 patients (5%) were removed since they did not present any purchase of ACE, ARB, BB or AA during the observation period. Further, since their health residence district was not in FVG region, other 146 (0.7%) patients were excluded. Thus, a total of 12,938 (63%) patients met study selection criteria (Figure 1.2).

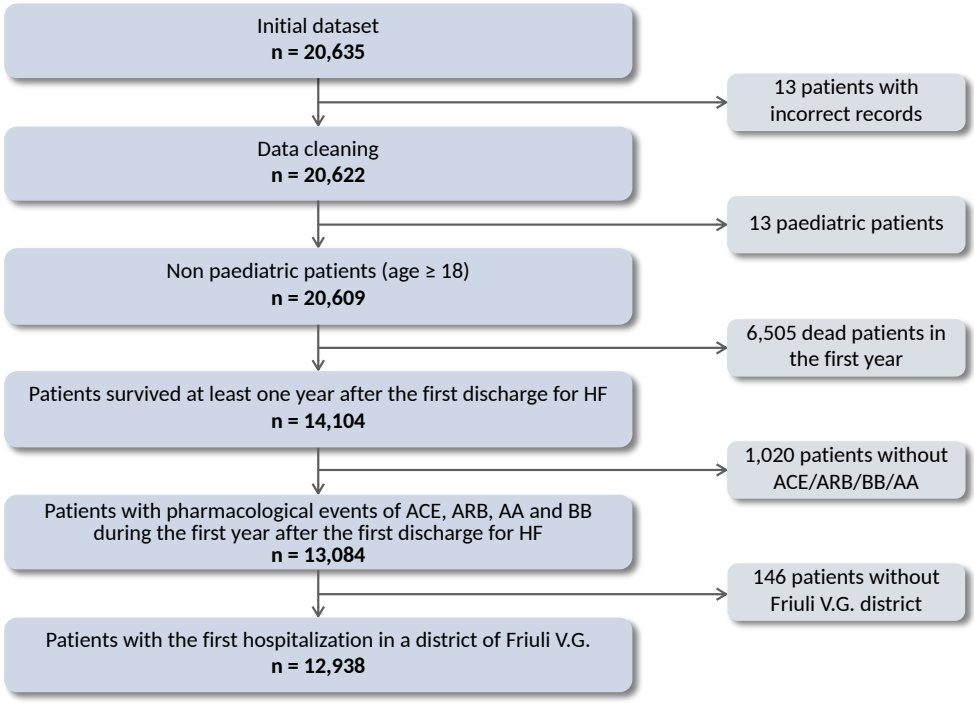

Figure 1.2. Flowchart of patient selection.

Overall, at index hospitalization (Table 1.2) mean age was 80 years with a substantial proportion of female patients (53.1%), high prevalence of *De Novo* patients (89.1%). Percentage of patients who have undergone at least one major procedure was 3.2%. Comorbidity burden was high (median of Charlson index 2; 46.8% of patients presenting Charlson index ≥ 3). The rate of discharge from Cardiological Ward (CW) was 10.3%. In the 24 months before the index hospitalization, 6,030 (46.6%) patients underwent a cardiological visit and 3,212 (24.8%) an echocardiogram.

Regarding pharmacological treatments, Figure 1.3 shows percentages of purchase of medications at discharge according to monotherapy, dual therapy or triple therapy. In monotherapy the most common purchased drugs were BB (71%) and the less ones were ARB (27.1%, light-blue columns); ACE or ARB (ACE/ARB) was purchased by 83.2% of patients. Regarding polypharmacy, the most common prescribed drugs were ACE or ARB and BB (58.1%) and the less frequent were ARB and AA (11.5%, blue columns). Finally, the triplet ACE or ARB, BB and AA was purchased by 27.3% of patients (purple column).

At the end of the observation period, i.e., one year after the index HF hospitalization (Table 1.3), mean age was 81 years and the median of Charlson index remained high (median of Charlson index 2; 47.4% with a Charlson index ≥ 3). Starting from the end of the observation period, during a median follow-up of 33 (IQR = [17.1; 55.1]) months, 7,752 (59.9%) patients died. In the 24 months before the last hospitalization of the observation period, 6,786 (52.5%) patients underwent a cardiological visit and 4,227 (32.7%) an echocardiogram. In the observation period, 53.6% patients were re-hospitalized

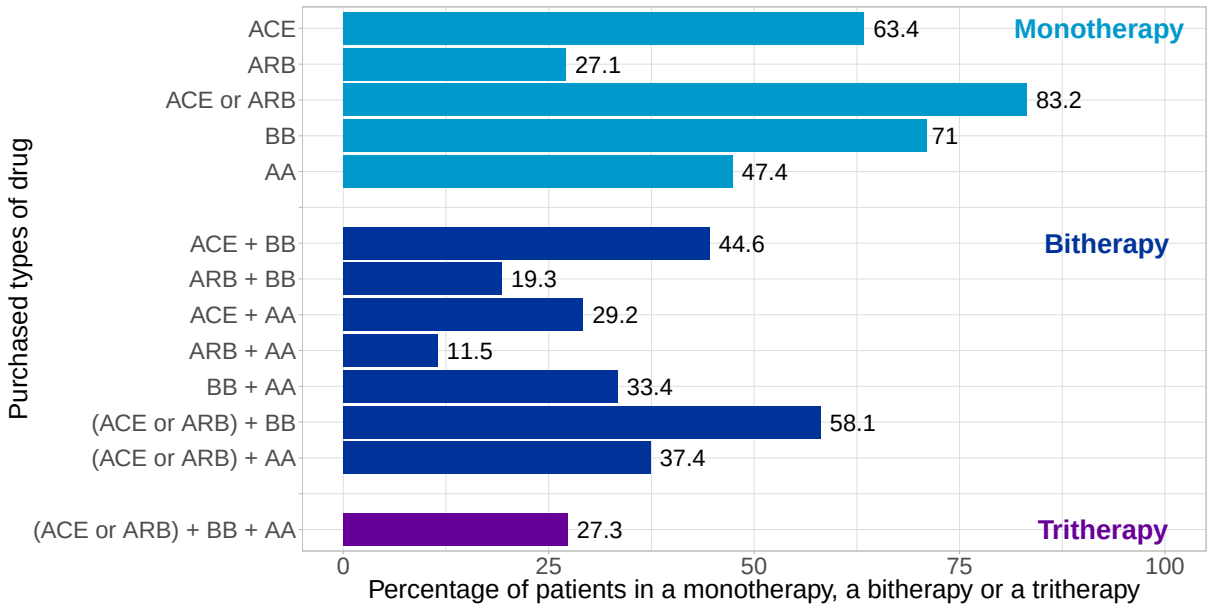

Figure 1.3. Barplots of percentages of patients in a monotherapy, a bitherapy or a tritherapy. Each column is related to the purchase of specific types of drug (i.e., ACE, ARB, ACE/ARB, BB, AA). On the top, light-blue columns show percentages about monotherapy, where 'ACE or ARB' means that a patient presents at least one purchase for ACE and/or ARB during the observation period. Central dark-blue columns show percentages about bitherapy and 'ACE + BB' means that a patient presents at least one purchase both for ACE and for BB during the observation period. On the bottom, the purple column shows the percentage about tritherapy and states that 27.3% of the whole cohort purchased ACE and/or ARB, BB and AA.

Table 1.2. Descriptive analysis of the whole cohort at index HF hospitalization.

Variable characteristics at index HF hospitalization	
Study Cohort	12,938 pts
Age [year]	
Mean (s.d.)	79.77 (9.62)
Gender	
Female (%)	6,875 (53.1%)
Male (%)	6,063 (46.9%)
HF Condition	
De Novo (%)	11,531 (89.1%)
Worsening (%)	1,407 (10.9%)
Number of procedures*	
0 (%)	12,440 (96.1%)
1 (%)	411 (3.2%)
2 (%)	62 (0.5%)
3 (%)	25 (0.2%)
≥ 4(%)	0 (0%)
Charlson index	
median (IQR)	2 (1; 4)
< 3	6,878 (53.2%)
≥ 3	6,060 (46.8%)
Cardiological Ward	
No (%)	11,602 (89.7%)
Yes (%)	1,336 (10.3%)
Cardiological visit	
No (%)	6,908 (53.4%)
Yes (%)	6,030 (46.6%)
Echocardiogram	
No (%)	9,726 (75.2%)
Yes (%)	3,212 (24.8%)
Creatinine**	
Median (IQR)	1.09 (0.89; 1.38)
Missing values (%)	1,599 (12.4%)
Glycated haemoglobin**	
Median (IQR)	6.6 (6.0; 7.5)
Missing values (%)	10,084 (77.9%)
Haemoglobin**	
Median (IQR)	12.3 (11.0; 13.6)
Missing values (%)	3,879 (30.0%)

Age, gender, number of procedures, Charlson index, laboratory tests and discharge from CW refer to the first event, the index hospitalization. Cardiological visit and echocardiogram refer to the 24 months before the index hospitalization. HF condition refers to the 5 years preceding the index admission.

* Examined major procedures: coronary angiography, Percutaneous Transluminal Coronary Angioplasty (PTCA) (w/out implantation of stent in coronary artery), Coronary Artery Bypass Graft surgery (CABG), implantation of pacemaker, cardioverter defibrillator or Cardiac Resynchronization Therapy (CRT), Transcatheter Aortic Valve Implantation (TAVI) or percutaneous mitral valve repair with MitraClip device. For the descriptive of each procedure, see supplementary material of Spreafico *et al.* (2020) [187].

** Laboratory tests: median values (if available) of creatinine, glycated haemoglobin and haemoglobin measured during the index hospitalization. Creatinine and glycated haemoglobin values were integrated to hospital diagnosis in the Charlson index computation.

Table 1.3. Descriptive analysis of the whole cohort at the beginning of follow-up period.

Variable characteristics at index HF hospitalization	
Study Cohort	12,938 pts
Age [year]	
Mean (s.d.)	80.77 (9.62)
Follow-up time [months]	
Median (IQR)	33 (17.1; 55.1)
Death	
0 (%)	5,186 (40.1%)
1 (%)	7,752 (59.9%)
Charlson index*	
median (IQR)	2 (1; 4)
< 3	6,801 (52.6%)
≥ 3	6,137 (47.4%)
Cardiological visit**	
No (%)	6,152 (47.5%)
Yes (%)	6,786 (52.5%)
Echocardiogram***	
No (%)	8,711 (67.3%)
Yes (%)	4,227 (32.7%)
Number of all-cause re-Hospitalizations	
0 (%)	6,006 (46.4%)
1 (%)	3,462 (26.8%)
2 (%)	1,775 (13.7%)
≥ 3 (%)	1,695 (13.1%)
Number of HF re-Hospitalizations	
0 (%)	10,422 (80.7%)
1 (%)	1,896 (14.7%)
2 (%)	437 (3.4%)
≥ 3 (%)	163 (1.2%)
Number of ICU services	
0 (%)	11,356 (87.7%)
1 (%)	1,305 (10.1%)
≥ 2 (%)	277 (2.2%)
IHC activation	
No (%)	8,718 (67.4%)
Yes (%)	4,220 (32.6%)
Dead patients cohort	7,752 pts
HF Condition‡	
De Novo (%)	6,563 (84.7%)
Worsening (%)	1,189 (15.3%)

ICU = Intermediate Care Unit, IHC = Integrated Home Care.
Age and gender refer to the end of the observation period (i.e., 365 days after the index hospitalization). Charlson index refers to the last hospitalization during the observation period. Cardiological visit and echocardiogram refer to the 24 months before the last hospitalization of the observation period. Number of re-hospitalizations, number of ICU and IHC activation refer to the observation period.
* Wilcoxon test with respect to the index date: p-value < 0.0001
** McNemar test on paired proportions with respect index date: p-value < 0.0001
*** McNemar test on paired proportions with respect index date: p-value < 0.0001
‡ Chi-square p-value < 0.0001

at least once for any-cause, 13.7% for two times and 13.1% more than two times. In particular, 19.3% of patients were re-hospitalized at least once for HF. Moreover, 12.3% of patients was admitted in ICU and IHC was activated at least once in 32.6% (4,220 patients) of the study cohort. Of note, for patients without any re-hospitalization during the observation period, the last hospitalization coincided with the index hospitalization.

1.3.2. Standardized Daily Dose

Figure 1.4 shows the standardized Daily Dose (sDD) of the main active principles under study. We investigated ramipril, enalapril and lisinopril among ACE; losartan, valsartan, olmesartan, telmisartan and candesartan among ARB; spironolactone, potassium canrenoate and canrenone among AA; bisoprolol, carvedilol, metoprolol and nebivolol among BB. Figure 1.4 shows distribution of sDD in our cohort by means of boxplots. To put the target dosages in evidence, we considered both 100% (blue lines) and 80% (orange lines). Considering 100% as the perfect target could be inappropriate, given the existence of some dynamical processes like up-titration of the drugs dosages that cannot be investigated through these data. So, we decided to consider also 80% as target in order to take into account these unknown processes and having a more realistic estimate of patients that actually reach target dosages. Percentages of patients with sDD $>$ 80% were 11.6%, 28.9% and 32.3%, for ramipril, enalapril and lisinopril, respectively. Percentages of patients with sDD $>$ 80% were 1.8%, 8.8%, 10%, 30.5% and 10.6%, for losartan, valsartan, olmesartan, telmisartan and candesartan, respectively. Percentages of patients with sDD $>$ 80% were 34.2%, 43.7% and 29.5%, for spironolactone, potassium canrenoate and canrenone, respectively. Percentages of patients with sDD $>$ 80% were 4.3%, 10.4%, 14.4% and 2.4%, for bisoprolol, carvedilol, metoprolol and nebivolol, respectively.

1.3.3. Patients' adherence measures

Using PDC, at the end of the observation period 47.2% of 8,199 ACE patients, 39.7% of 3,503 ARB patients, 22.6% of 9,183 BB patients, 18.3% of 6,137 AA patients and 48.5% of 10,759 of ACE or ARB patients were adherent to the corresponding treatment at the threshold of 80% (see Table 1.4). Using MPR measure, percentages were higher: 63% of ACE patients, 58.5% of ARB patients, 36% of BB patients, 31.5% of AA patients and 66% of ACE or ARB patients.

Descriptive statistics about adherence to polypharmacy indices of the study cohort are reported in Table 1.5. Using PDC, the following PAI values emerged: 47.2% (0: non-adherent patients), 11.1% (1/3), 20.5% (1/2), 5.1% (2/3) and 16.1% (1: fully adherent patients). Consequently, 41.7% of the patients had *good* percentage of adherence to polypharmacy (n = 5,393). Using MPR, the following PAI values were calculated: 29.1% (0: non-adherent patients, n = 3,758), 11.4% (1/3), 23.8% (1/2), 8.8% (2/3) and 26.9% (1: fully adherent patients). Consequently, 59.5% of the patients had *good* percentage of adherence to polypharmacy (n = 7,700). Of note, in Table 1.6 we provided information

about the number of purchased drugs and the percentage of poly-adherent patients. As expected, we observe that the higher is the number of therapies, the lower is the poly-adherence (both p-values are less than 0.0001).

Table 1.4. Numbers and percentages of adherent patients to the corresponding treatment at the threshold of 80% using both PDC and MPR measures.

Adherent		**ACE**	**ARB**	**BB**	**AA**	**ACE/ARB**
Cohort	no. pts	8,199	3,503	9,183	6,137	10,759
PDC	No (%)	4,325 (52.8%)	2,112 (60.3%)	7,110 (77.4%)	5,015 (81.7%)	5,544 (51.5%)
	Yes (%)	3,874 (47.2%)	1,391 (39.7%)	2,073 (22.6%)	1,122 (18.3%)	5,215 (48.5%)
MPR	No (%)	3,030 (37.0%)	1,454 (41.5%)	5,874 (64.0%)	4,202 (68.5%)	3,661 (34.0%)
	Yes (%)	5,169 (63.0%)	2,049 (58.5%)	3,309 (36.0%)	1,935 (31.5%)	7,098 (66.0%)

Table 1.5. Descriptive analysis of Patient Adherence Indicators (PAIs) of the whole cohort.

PP Index	**PP scale**	**PDC**	**MPR**
PAI	0 (%)	6,107 (47.2%)	3,758 (29.1%)
	1/3 (%)	1,438 (11.1%)	1,480 (11.4%)
	1/2 (%)	2,653 (20.5%)	3,080 (23.8%)
	2/3 (%)	654 (5.1%)	1,139 (8.8%)
	1 (%)	2,086 (16.1%)	3,481 (26.9%)
PAI group	*good* (%)	5,393 (41.7%)	7,700 (59.5%)
	poor (%)	7,545 (58.3%)	5,238 (40.5%)

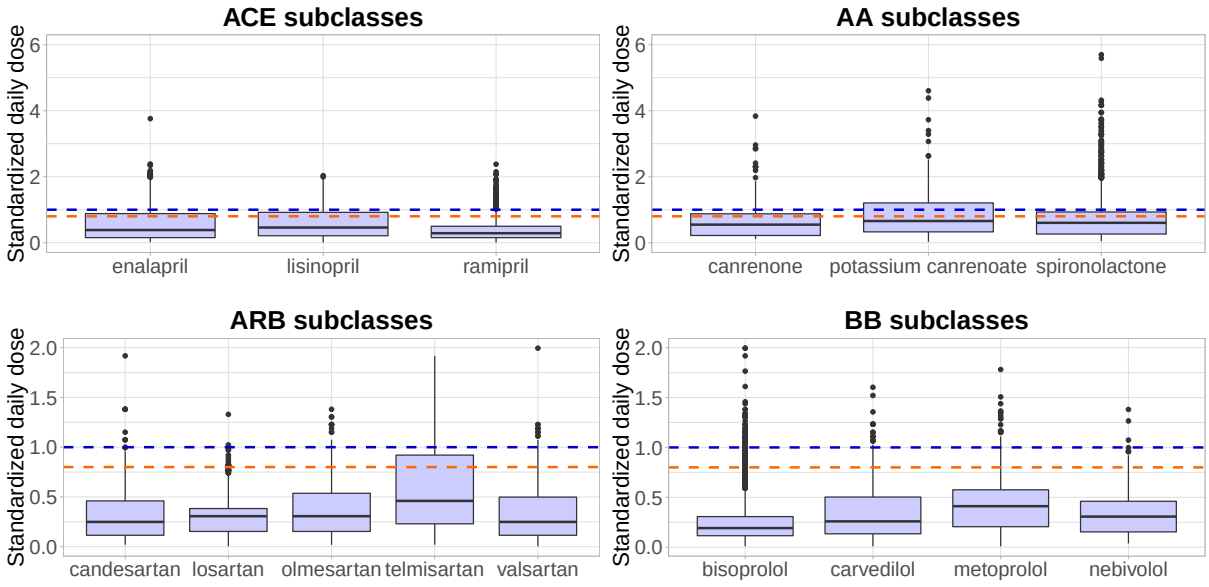

Figure 1.4. Boxplots of standardized Daily Dose (sDD) for the main active principles of each pharmacological class. Top-left panel reports ACE main subclasses: enalapril, lisinopril and ramipril. Top-right panel reports AA main subclasses: canrenone, potassium canrenoate and spironolactone. Down-left panel reports ARB main subclasses: candesartan, losartan, olmesartan, telmisartan and valsartan. Down-right panel report BB main subclasses: bisoprolol, carvedilol, metoprolol and nebivolol. Dashed blue lines (standardized daily dose = 100%) indicate that the mean purchased DD are equal to the respective target dosages recommended in the ESC Guidelines [139, 50] or according to clinical practice of AIFA's website [4]. Dashed orange lines (standardized daily dose = 80%) indicate that the mean purchased DD are equal to the 80% of the respective target dosages.

Table 1.6. Numbers and percentages of Poly-Adherence (PA), computed both with PDC and MPR, with respect to number of different types of purchased drugs (i.e., PI, Purchase Indicator).

			Poly-Adherence (PA) with PDC			
		no. pts	**0**	**1**	**2**	**3**
Purchase Indicator (PI)	**1**	3,331	2,068 (62.1%)	1,263* (37.9%)	Not possible	Not possible
	2	6,073	2,699 (44.4%)	2,653 (43.7%)	721 * (11.9%)	Not possible
	3	3,534	1,438 (37.9%)	1,438 (40.7%)	654 (18.5%)	102 * (2.9%)
			Poly-Adherence (PA) with MPR			
		no. pts	**0**	**1**	**2**	**3**
Purchase Indicator (PI)	**1**	3,331	1,577 (47.3%)	1,754 ** (52.7%)	Not possible	Not possible
	2	6,073	1,562 (25.7%)	3,080 (50.7%)	1,431 ** (23.6%)	Not possible
	3	3,534	619 (17.5%)	1,480 (41.9%)	1,139 (32.2%)	296 ** (8.4%)

* Test for proportions of global Poly-Adherence (1263/3331, 721/6073, 102/3534): p-value < 0.0001.
** Test for proportions of global Poly-Adherence (1754/3331, 1431/6073, 296/3534): p-value < 0.0001.

1.3.4. Multivariable Cox models for survival outcome

In Table 1.7 impact of covariates on survival for each Cox model is displayed. Among risk factors we identified: WHF, age, Charlson score, re-hospitalizations, ICU and IHC. Specifically, being a WHF patient with respect to a De Novo patient, being elder, having a higher Charlson index, being re-hospitalized more often, being admitted in ICU and the activation of IHC implied a higher risk of death. Conversely, among protective factors we identified: the discharge from a Cardiological Ward (CW) in the index hospitalization and a cardiological visit in the 24 months before the last hospitalization of the observation period. Regarding polypharmacy indices, both PAI (first and second model) and PAI group (third and fourth models) were significantly protective (HRs < 1). In particular, higher values of PAI and being labelled as *good* in case of PAI group were associated with a lower risk of death.

Figure 1.5 shows this result through the estimate of a survival curve stratified by *good* and *poor* levels in the case of PAI group computed using PDC (third model) for a hypothetical patient that should be representative of the studied cohort. Specifically, we considered a 82-years old, female, De Novo patient with a previous cardiological visit and a Charlson index (at the last hospitalization) equal to 2. Moreover, at index HF hospitalization this patient was not discharged from CW and during the observation period she was re-hospitalized only once and did not benefit of any ICU service or IHC activation. These values correspond to the medians of the continuous variables and the modes of the categorical variables measured in our cohort.

Table 1.7. Adjusted Hazard Ratios with 95% Confidence Intervals (CI) and p-values of each Cox's model. Each column corresponds to a different Cox regression models, one for each of the following polypharmacy indices: PAI and PAI group computed with both PDC and MPR adherence results.

	Model 1 – PDC		**Model 2 – MPR**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
HF Condition [WHF]	1.24 [1.16; 1.32]	6.77e-11	1.24 [1.16; 1.32]	7.33e-11
Age	1.06 [1.06; 1.07]	< 2e-16	1.06 [1.06; 1.07]	< 2e-16
Gender (M]	1.32 [1.26; 1.39]	< 2e-16	1.32 [1.26; 1.39]	< 2e-16
Charlson index	1.11 [1.09; 1.12]	< 2e-16	1.11 [1.09; 1.12]	< 2e-16
CW	0.78 [0.71; 0.85]	1.97e-07	0.78 [0.71; 0.86]	2.39e-07
Cardiological visit	0.94 [0.89; 0.98]	0.00439	0.94 [0.90; 0.98]	0.00563
Re-hospitalizations	1.11 [1.10; 1.13]	< 2e-16	1.12 [1.10; 1.13]	< 2e-16
ICU services	1.14 [1.09; 1.20]	4.18e-08	1.14 [1.09; 1.20]	3.12e-08
IHC activation	1.27 [1.22; 1.34]	< 2e-16	1.28 [1.22; 1.34]	< 2e-16
PAI	0.91 [0.85; 0.97]	0.00270	0.94 [0.89; 0.99]	0.03819
	Model 3 – PDC		**Model 4 – MPR**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
HF Condition [WHF]	1.24 [1.16; 1.32]	9.33e-11	1.24 [1.16; 1.32]	7.97e-11
Age	1.06 [1.06; 1.07]	< 2e-16	1.06 [1.06; 1.07]	< 2e-16
Gender (M]	1.32 [1.26; 1.39]	< 2e-16	1.32 [1.26; 1.39]	< 2e-16
Charlson index	1.11 [1.09; 1.12]	< 2e-16	1.11 [1.09; 1.12]	< 2e-16
CW	0.78 [0.71; 0.85]	1.63e-07	0.78 [0.71; 0.85]	1.87e-07
Cardiological visit	0.94 [0.89; 0.98]	0.00466	0.94 [0.90; 0.98]	0.00572
Re-hospitalizations	1.11 [1.10; 1.13]	< 2e-16	1.11 [1.10; 1.13]	< 2e-16
ICU services	1.14 [1.09; 1.20]	3.73e-08	1.14 [1.09; 1.20]	3.20e-08
IHC activation	1.27 [1.22; 1.34]	< 2e-16	1.28 [1.22; 1.34]	< 2e-16
PAI group (good]	0.93 [0.88; 0.97]	0.00119	0.93 [0.89; 0.98]	0.00354

Each model was adjusted for nine time-independent covariates: HF condition and discharge from CW at index hospitalization, cardiological visit in the 24 months before the last hospitalization of the observation period, number of re-hospitalizations, number of ICU services and IHC activation during the observation period, Charlson index at the last hospitalization, age and gender at the beginning of the follow-up period.

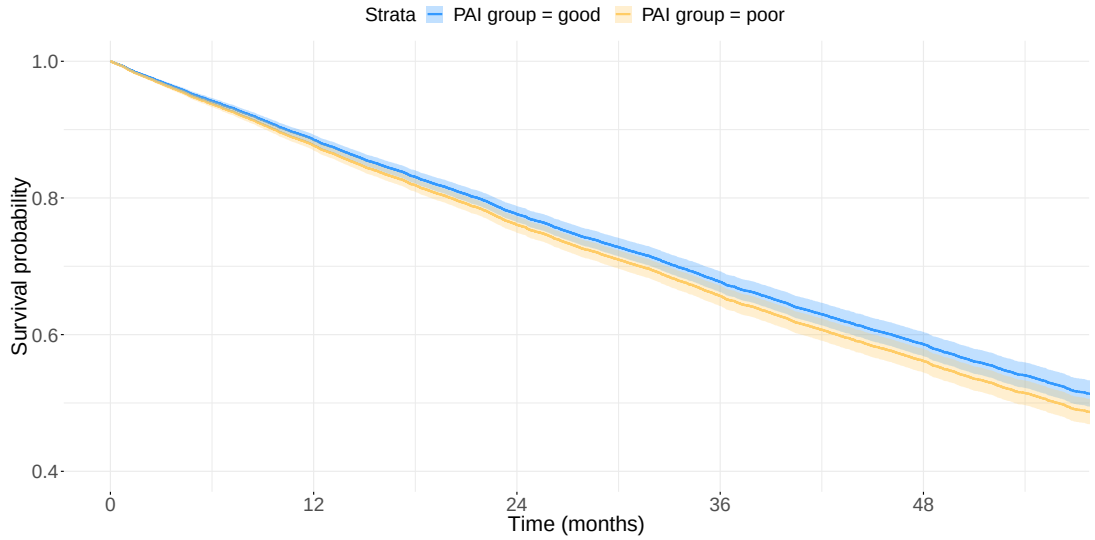

Figure 1.5. Estimated survival from the Cox model stratified by *good* and *poor* patients in the case of PAI group computed using PDC. Adjusting covariate values are the medians of the continuous variables and the modes of the categorical variables measured in our cohort: female-De Novo patient aged 82 years old with a Charlson index at the last hospitalization equal to 2; at index hospitalization this patient was not discharged from Cardiologic Ward; during the observation period she was re-hospitalized only once time, she did not benefit of ICU service or IHC activation, and she underwent one cardiological visit.

1.4. Final remarks

The goal of Drug Utilization Research [220] is to facilitate the rational use of drugs in patient populations. A key point emerged from clinical trials is that the prescription of drugs should be in the "optimal" dose for the therapeutic indication. To date, few data exist regarding the adherence to drug therapies in a real world setting for HF patients. Indeed, most of previous data have been focused on physician's prescription adherence to recommended medications in HF patients [108, 130]. In the present chapter, we took advantage of real-world pharmacological records about drugs purchases in order to have a proxy of patient's adherence to polypharmacy.

Our study confirmed that, even when prescriptions of guideline-based HF treatment are high, there is evidence of frequent failures to reach target doses [130]. In fact, results showed high proportion of HF patients were treated with low dosages of recommended therapies: mean daily dosages purchased by patients were well below the target dosages for all the drugs considered. Data from quality surveys reported similar trend in the prescriptions, with less than one-third of patients on guideline-recommended target dosages [108]. Similarly, a recent European survey (BIOSTAT-CHF) conducted in 11 countries and enrolling 2,500 patients showed that only a minority of patients reached the target dose of ACE and BB [148]. These trends confirmed that simple calculation of the percentage of "treated" patients based on physician's prescription might not be an adequate measure to indicate the quality of healthcare provided for HF patients.

In addition, patients' adherence to oral treatment of HF medications was widely unsatisfactory, in particular taking into account the PDC approach (47% of non-adherent

patients, PAI index based on PDC). This is in contrast to physician's prescriptions of appropriate classes of therapy that instead has improved considerably over the past decade, from approximately a quarter of prescriptions in 2008 to nearly two thirds in 2016 [107]. In particular, we focused on patient's adherence in 1-year from an HF hospitalization. In this observation period, we found that treatment with the association of oral BB, ACE/ARB and AA was present in one-third of patients, and percentages of patients adherent to only one or two drugs out of three prescribed ranged from 16% to 20% (PAI index computed for 1/3 or 2/3 cases).

Our study indicated that the risk of death significantly decreased in presence of a good adherence to polypharmacy. Importantly, we reported adherence measures on effective purchases exploiting the potential of administrative healthcare databases. The proposed index PAI can be viewed as a modified version of the Guideline Adherence Indicator, GAI, [225] based only on physician's prescriptions at discharge and not on effective patient's purchases and adherence patterns. The significant PAI effect on survival suggests that medication non-adherence is associated with lower survival probability also in the case of polypharmacy therapy, so extending previous results about the effect of non-adherence to specific drugs classes [148].

The two methods of adherence calculations – based on PDC and MPR – showed some relevant differences in terms of percentages of adherent patients for the specific single-drug classes. These differences are due to the fact that adherence could be underestimated by measures which ignore overlaps (i.e., PDC) and overestimated by ones which count overlaps (i.e., MPR) during the observation period. In the current literature, PDC has been suggested as the preferred method to reflect adherence of patients who are prescribed multiple medications concurrently within a class [133] and recently a modified MPR calculation has been proposed in the context of polypharmacy [17]. Noteworthy, we did not observe relevant prognostic differences when PDC or MPR-based measures were combined in the PAI index. This could indicate that adherence to drugs combinations is prognostically more relevant, irrespective from the single-class measure adopted.

To the best of our knowledge, only one very recent paper published in 2018 tackled the issue of polypharmacy adherence in a cardiovascular setting and proposed a novel index [17]. Specifically, they introduced a new "daily polypharmacy possession ratio" (DPPR) based on Australian pharmaceutical benefits scheme database. This work [17] is of great interest, however it is not clear how much the obtained results are affected by the initial strong selection procedure; indeed, they excluded more than half of the cohort based on patients age. This procedure would lead to a not negligible selection bias in our cohort. In line with previous real-word studies focused on HF [59, 94, 93] our population included a high proportion of elderly patients and women, with high rates of non-cardiac comorbidities. Of note, this could also explain the large proportion of HF patients discharged from non-cardiological ward.

Some limitations of the present study have to be noted. First of all, in the healthcare administrative archives no socio-economic data and no clinical data about New York Heart Association (NYHA) class or Left Ventricular Ejection Fraction (LVEF) were available.

Therefore, it was not possible to stratify patients according to clinical HF severity; as a proxy, we used previous HF hospitalization in the patient history. Another limitation is the absence of a specific analysis on diuretics adherence. Although the topic is intriguing, patients' adherence to diuretics is hard to evaluate without clinical data, since their modulation to fluid overload. Since the lack of physician's prescriptions (at discharge and during follow-up) and the possible development of drugs adverse reactions, several concerns remain on the estimated rate of patient's non-adherence. Dedicated future studies are encouraged on this topic integrating clinical and administrative sources of data. Then, in the PDC and MPR computations, theoretical Defined Daily Doses (DDD) were used instead of Prescribed Daily Doses (PDD) and therefore a bias could be present in the estimated adherence if the underlying PDD/DDD ratio is different from 1 [220, 69]. Moreover, the cut-off of PDC or MPR greater than 80% to define patient adherence could be further examined in a sensitivity analysis in order to find if other values or a distribution of thresholds could better stratify patient's outcome. Finally, some technical improvements may be included into the PAI definition in order to provide a more elaborated formula which is able to reward more patients that are adherent to polypharmacy with respect to those adherent in monotherapy. In the present definition of PAI a patient scores 1 if he/she is fully adherent to only one drug or if he/she is fully adherent to a combination of drugs. For example, the PAI definition could be modified combining the terms with some weights, in order to maximize the predictive capacity of the model and producing a more refined grading score among patients.

To summarize, the main purpose of the present chapter was to describe guidelines compliance in a real-world HF community and evaluate the impact of combined drugs adherence on survival. Patients' adherence remained widely unsatisfactory especially taking into account attainment of target dosages and polypharmacy. Adjusting for patient's characteristics and intermediate events, good adherence to polypharmacy in the first year after HF hospitalization was associated with improved survival, irrespective of the specific measure of single drug class adherence used. Although the PAI index represents a first step forward in the assessment of adherence to polypharmacy using real-world data, it exploits the PDC/MPR measures which are *time-fixed* indexes computed at the end of the observation period, without taking into account changes in patient drug utilization behaviour over time. In addition to discarding valuable information, this can lead to selection bias due to the exclusion from the study cohort of patients who did not survive the first 1-year period. To overcome this problem, it is necessary to explore alternative statistical approaches that model adherence as a time-varying covariate, as we shall see in the next chapter.